Paradoxical effects of the topoisomerase inhibitor, ethoxidine, in the cellular processes leading to angiogenesis on EaHy.926 endothelial cells

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Résumé en anglais	Topoisomerase I generates transient single-stranded breaks in DNA and have the capacity to fragment the genome. Thus, this enzyme is the target for some of the most successful anticancer drugs. Ethoxidine, a benzo[c]phenanthridines derivative, was identified as a potent inhibitor of topoisomerase I. As angiogenesis is a critical step in tumorigenesis, this study was designed to test the potential effect of ethoxidine on different processes leading to neovascularisation on EaHy endothelial cells including adhesion, migration and proliferation. Ethoxidine was tested at two concentrations, 100 µM and 10 µM . VEGF (20 ng/mL) was used as control. Adherent cells were evaluated using crystal violet staining, migration using a model of wound healing. Proliferation was analyzed using CyQUANT Cell Proliferation Assay Kit. Both $O_2^{\cdot}$ and NO productions were assessed using electronic paramagnetic resonance technique. All the effects of ethoxidine were evaluated at 24 h treatment. Low concentration of ethoxidine promoted migration to the same extent as that produced by VEGF whereas high concentration inhibited this process. Ethoxidine significantly enhanced adhesion at similar level than VEGF at low concentration. It was without effect at high concentration. Although ethoxidine had no effect at low concentration, it significantly reduced cell proliferation at high concentration. At any concentration tested, ethoxidine did not modify basal $O_2^{\cdot}$ production. Interestingly, ethoxidine significantly increase NO production at low concentration but it was without effect at high concentration. As control experiment, VEGF enhanced Eahy cells NO production under the same experimental conditions. Altogether, the present study highlights paradoxical effects of ethoxidine depending on the concentration used. At low concentration, it promotes both Eahy cells migration and adhesion without any effect on proliferation. Importantly, these effects were associated with an increase of NO production. In contrast at high concentration, ethoxidine reduced Eahy cells migration and proliferation but had no effect neither on adhesion nor NO release. Of note is the fact that ethoxidine did not alter endothelial cells oxidative stress at any concentration tested. Thus, these data underscore the potential anti-tumoral property of ethoxidine at high concentration and endothelial cells in the present study. The property of ethoxidine in inhibiting proliferation in both cell type probably account for its high antitumor activity.
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